REMARKS

The Office Action of June 25, 2010 constitutes a non-final rejection of the claims. The Office Action and the references relied upon therein have been carefully reviewed. Reconsideration and allowance of the claims are requested in view of the foregoing amendments and the following remarks.

I. Claim Status and Amendments

Claims 24, 26, 28, 29, 31, 32 and 34-37 presently appear in this case. Claims 28 and 31 are currently withdrawn from consideration as being drawn to non-elected subject matter. Claims 24, 26, 29, 32 and 34-37 have been examined on the merits and stand rejected.

By way of the present amendment, claim 29 has been cancelled without prejudice and claim 36 has been amended to recite "Copolymer 1", instead of "Copolymer", to thereby correct a typographical error. No new matter has been added.

Claims 24, 26, 28, 31, 32 and 34-37 are pending upon entry of this amendment.

II. Claim objections

Claim 36 has been objected for reciting "Copolymer" in line 7, instead of "Copolymer 1". In response, claim 36 has been amended, by way of the present amendment, to recite "Copolymer 1" to thereby render the objection moot.

III. Enablement Rejections

Claims 24, 26, 29, 32, and 34-37 have been rejected under 35 USC §112, first paragraph, on the grounds that the specification, while being enabling for treating neuronal degeneration caused by glutamate toxicity or $A\beta_{1-40}$ toxicity in an animal model, does not reasonably provide enablement for treating or reducing progression of a neurodegenerative disease, such as Huntington's disease (HD), or preventing neurodegeneration associated with HD, for the reasons set forth on pages 2-8 of the Office Action. The rejection is respectfully traversed.

The examiner argues that the disclosure in the specification of effective results in animal models, such as R6/2 transgenic mice, for HD, does not necessarily translate into human treatment.

The examiner reiterates his points made in the previous Office Action in that the state of the art is low with regard to treatment of HD and that there is no known agent that is effective in treating HD, and cites the website for Huntington's Disease Society of America (www.hdsa.org/about/ourmission/what-is-hd.html), which discloses that at present there is no effective treatment to halt the progression of HD or cure for HD.

The examiner is further of the opinion that due to the unpredictability of treatment of neurodegenerative disease, the limited disclosure in the application for animal model of glutamate toxicity is not sufficient to justify claiming a broad method of treatment of HD.

The examiner has considered the arguments in the Amendment filed April 8, 2010 in response to the previous Office Action but has not found them persuasive. Previously, Applicants argued that the specification provides support for use of the HD R6/2 mouse model of HD, in which mice over-express exon 1 of the human Huntington's disease gene, and this model has been used widely as an animal model of human HD. Yet, at the bottom of page 5 of the Action, the examiner argues that this model is not the same as human HD, and considering the unknown etiology of HD, and that the HD gene, huntingtin, is one identified characteristic of HD, the disclosed R6/2 animal model cannot be considered the same as human HD. The examiner contends that it would not be predictable whether treatment of the animal model would necessarily work in real HD without undue experimentation.

At the bottom of page 6 of the Action, the examiner argues that in order to obtain validity for human treatment of the efficacy resulted from animal models, human clinical

trials are needed, which are not routine experimentation and which do require extensive and undue experimentation.

The examiner cites Bates et al. as allegedly supporting the rejection. The examiner contends that Bates et al. disclose that animal models, including R6/2 transgenic mice, would be useful tools to identify therapeutic compounds but would only be validated once they have delivered a therapy that shows efficacy in the clinic. Additionally, the examiner states that Bates et al. further suggests that the first successful treatments for HD might be composed of combinations of drugs each of which makes a small contribution to the overall beneficial effect. The examiner then argues that even though the current invention shows effectiveness of compounds in animal models of HD, these results would not necessarily translate into efficacy in the clinic. The examiner concludes that the current invention does not enable a person skilled in the art to use the invention without undue experimentation.

Applicants respectfully disagree and submit that the claimed methods for treating Huntington's disease, for reducing disease progression, for protection from neurodegeneration and/or protection from glutamate toxicity in Huntington's disease, and for treating or preventing neurodegeneration and cognitive decline and dysfunction associated with Huntington's disease, comprising administering

to an individual an active agent selected from the group consisting of (i) Copolymer 1, (ii) a Copolymer 1-related peptide, (iii) a Copolymer 1-related polypeptide, and (iv) T cells activated with (i), (ii) or (iii), are fully enabled and supported by the disclosure in the application for at least the following reasons.

According to US practice, as enumerated at MPEP §2107.03, evidence presented to support a claim for treatment of a disease will be relevant if there is a reasonable correlation between the claimed use and the evidence presented. In this regard, MPEP §2107.03 states as follows:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is

> required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).
>
> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. [Emphasis added.]

Additionally, MPEP §2107.03 discloses that the model presented should only be reasonably predictive, and absolute certainty is not required. It is also stated that the mere fact that something has not been done (for example, treatment for HD has not yet been found), is not a sufficient basis for rejecting a disclosure teaching how to do it. In particular, MPEP §2107.03 states as follows:

> Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. Thus, an applicant may provide data generated using a particular animal model with an appropriate explanation as to why that data supports the asserted utility. The absence of a certification that the test in question is an industry-accepted model is not dispositive of whether data from an animal model is in fact relevant to the asserted

> utility. Thus, if one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility. *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *Ex parte Krepelka*, 231 USPQ 746 (Bd. Pat. App. & Inter. 1986). Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application. See *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956) ("The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."); *In re Wooddy*, 331 F.2d 636, 639, 141 USPQ 518, 520 (CCPA 1964) ("It appears that no one on earth is certain as of the present whether the process claimed will operate in the manner claimed. Yet absolute certainty is not required by the law. The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."). [Emphasis added.]

Further guidance on this point can be found at MPEP §2164.02, which expands on the issue of correlating *in vitro* and/or *in vivo* data with the claimed method. MPEP §2164.02 states:

> An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this

> regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

In addition, MPEP §2107.03 further states that clinical trials are not required to support a claimed method for treatment of humans, as follows:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art recognized animal models existed for the human disease encompassed by the claims. [Emphasis added.]

Accordingly, contrary to the examiner's position, US case law clearly establishes that human clinical trials are not necessary in order for the claimed method of treatment to be patentable. More importantly, it is believed that the

guidance and *in vivo* animal model data presented in the instant application are reasonably correlated with and predictive of therapeutic treatment of Huntington's disease in humans for the reasons discussed herein below.

With respect to treating Huntington's disease, the specification discloses several examples for methods of using Copolymer 1 in the treatment of animal model systems. Example 1 on page 25 shows that treatment with Copolymer 1 provides neuroprotection from the effects of glutamate toxicity in C57Bl/6J mice. Example 3 on page 29 shows that administration of Copolymer 1 results in a significant improvement in the motor performance of R6/2 mice and delayed mortality and onset of diseases in R6/2 mice.

Also provided, together with results from Examples 1 and 2, is a human adult dose conversion and a detailed dose regime.

As argued in the last response, the R6/2 mouse model for Huntington's disease (as used in the examples of the instant application) is the most widely used animal model, and shares many characteristics with Huntington's disease. This is supported by Carter *et al.*, The Journal of Neuroscience, 19(8):3248-3257 (1999), and Björkqvist *et al.*, Human Molecular Genetics, 14(5): 565-574 (2005) (copies of which are being submitted herewith and being cited in IDS being filed

concurrently herewith). See the Abstract on page 3248 of Carter et al., wherein it is disclosed that the R6/2 mouse animal model develops a progressive neurological phenotype with motor symptoms resembling those seen in HD. See also, page 3256, left column, second to last paragraph, of Carter et al., wherein it is stated that the R6/2 mouse model offers a unique system in which the testing of experimental treatments for HD can be performed. See also page 566, second paragraph on the left-hand column of Björkqvist *et al.*, wherein it is disclosed that the R6/2 mouse model is used to study HD pathogenesis since it develops many neurological symptoms that resemble many of those seen in HD. These characteristics include deficits of motor coordination, altered locomotor activity, impaired cognitive performance and seizures.

Further, even the Bates et al. reference cited by the examiner supports Applicants' point. The Bates reference was cited by the examiner for allegedly disclosing that the animal model test used by Applicants has not always been predictive of clinical success. However, it should be noted that Bates indicates that this same test has, at some times, been successfully predictive. Further, at page 467, last paragraph on the right-hand column to page 468, first paragraph, Bates discloses that the R6/2 mouse model for Huntington's disease is the most extensively used animal model

for preclinical trials, and it is likely that this will continue.

In view of the above, it should be clear that the mouse R6/2 model (used in the working examples of the present application) is an art recognized animal model for HD treatment in humans. Indeed, the tests performed and the results obtained in the instant application, which show that treating with Copolymer 1 prevents the onset of disease, delays mortality (and therefore reduces disease progression) and improves motor function in the R6/2 mouse model, and provides neuroprotection in a mouse model for glutamate toxicity, reasonably correlates to and supports the claims directed to treatment of Huntington's disease in humans. In other words, based on the relevant evidence as a whole, there is a reasonable correlation between the art recognized *in vivo* animal model used in the disclosure and the claimed method of treatment. Again, absolute certainty is not required by the law.

To further prove this point, it should be noted that the USPTO has previously granted several patents with claims to treatment of Huntington's disease but without providing human clinical trial data to support such claims. Examples of such patents are discussed below:

- US 6,794,414 claims methods of treating disease mediated by transglutaminase (including HD) using the transglutaminase

inhibitor, cystamine. Cystamine is also disclosed on page 468, right-hand column, last paragraph of Bates *et al.* as a compound that has produced reproducible results in the R6/2 model. No clinical trial data is presented in this patent.

- US 7,220,729 claims methods for ameliorating the locomotor activity symptoms associated with Huntington's disease comprising administering CGS21680, which is not supported by human clinical data, but rather by experiments using the R6/2 mouse model.

- US 7,718,699 claims methods for the treatment of a group of diseases including HD comprising administering a therapeutically relevant amount of abscisic acid, which is supported by *in vitro* methods, without clinical trials.

- US 7,217,687 claims methods for treatment of neurological diseases including HD by administration of osteopontin or an agonist thereof, supported by cell lines and animal models (for Multiple sclerosis) but not by clinical trials.

- US 6,071,970 claims methods for the treatment of neurological disorders including HD by administering a certain formula, supported by experiments in mouse and rat tissues.

The above noted patents are being submitted cited in an IDS being filed concurrently herewith.

Thus, since the R6/2 mouse model is the most widely used animal model for HD, and is considered to be the most reliable animal model for Huntington’s disease, the positive data obtained in the instant application using this animal correlates to treatment of HD in humans. Further, based on the above-referenced patents, the USPTO clearly considers tissue culture experiments and animal models, which are less widely acknowledged for Huntington’s disease compared with R6/2, as appropriate support for claims reciting treatment of

HD, without requiring clinical trial data. For these reasons, it is believed that the treatment of R6/2 mice, as presented in the present application, should be considered as sufficient support for the present claims without requiring human clinical trial data. Again, clinical trial data is not required, as discussed at MPEP §2107.03. Therefore, it is believed that the claimed methods for treating of Huntington's disease, for reducing disease progression, for protection from neurodegeneration and/or protection from glutamate toxicity in Huntington's disease, and for treating or preventing neurodegeneration and cognitive decline and dysfunction associated with Huntington's disease, comprising administering to an individual an active agent selected from the group consisting of (i) Copolymer 1, (ii) a Copolymer 1-related peptide, (iii) a Copolymer 1-related polypeptide, and (iv) T cells activated with (i), (ii) or (iii), are reasonably supported by the specification.

Finally, it is again noted that in order to make an enablement rejection, the Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (i.e., the Office must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately

enabled by the disclosure). See MPEP § 2164.04. It is believed that the Office has not done so here. The examiner has not provided a sufficient rationale, nor has he provided an evidentiary basis, to disprove the demonstrated *in vivo* effectiveness of the claimed method of treatment. The examiner's arguments with respect to the alleged unpredictability in the field, including the contention that the state of the art is relatively low with regard to the treatment of HD do not negate the positive findings in the disclosure for treating the disease conditions using an art recognized animal model for the disease. There is simply no reason to believe that the results disclosed in the specification using the art recognized animal model cannot be extrapolated to humans to provide enablement for treating or reducing progression a neurodegenerative disease, such as HD.

As such, it is respectfully submitted that the skilled artisan could extrapolate from the results of the *in vivo* examples using an art recognized animal model for HD and the disclosed human dose conversion information to formulate an effective dosage to administer to humans to successfully perform the claimed method of treatment, without undue experimentation. Indeed, determining appropriate dosage levels is generally regarded as not requiring undue experimentation of persons of ordinary skill in the art. *In re*

Bundy, 642 F.2d 430, 209 U.S.P.Q. 48 (C.C.P.A. 1981). Thus, Applicants respectfully submit that the skilled artisan could practice the scope of the claims without undue experimentation.

For these reasons, the enablement rejection is untenable and should be withdrawn.

IV. Written Description Rejections

Claim 29 has been rejected under 35 U.S.C. § 112, first paragraph, for not complying with the written description requirement on the grounds that the specification does not support the claim language "therapeutically effective amount". The examiner argues contends that the specification does not disclose any amount of claimed compound for the effective outcome of reducing disease progression, protection from neurodegeneration or glutamate toxicity in HD patients.

For the sole purpose of expediting prosecution and not to acquiesce to the rejection, claim 29 has been cancelled without prejudice or disclaimer thereto. Thus, the present amendment renders the rejection moot. Withdrawal of the rejection is therefore requested.

IV. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action.

It is respectfully submitted that the claims are in condition for allowance and favorable action thereon is requested.

If the Examiner has any proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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Appendix:

The following documents are submitted concurrently herewith:

1. Carter *et al*., The Journal of Neuroscience, 19(8): 3248-3257 (1999);

2. Björkqvist *et al*., Human Molecular Genetics, 14(5): 565-574 (2005).